EBioMedicine 44 (2019) 12–13

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

GI distress: A breath of fresh air in respiratory homeostasis

Richard Kinkead *, Jean-Philippe Rousseau, Tara A. Janes

Department of Pediatrics, Université Laval, Centre de Recherche de l'Institut Universitaire de Cardiologie et Pneumologie de Québec, QC, Canada

Keywords:
Hypercapnia
Gut microbiota
Psychobiotics
Control of breathing

Unlike some subgroups of humans, bacteria live in "cultured" and highly diverse communities. About a decade ago, Sibley et al. [1] discovered that the composition of the bacterial population residing within the airways is an important determinant of lung infection severity and overall health of cystic fibrosis patients [1]. Accordingly, managing the composition of the microbial community was proposed to improve response to treatment when a given organism, such as *Pseudomonas aeruginosa*, becomes resistant to antibiotic therapy. Given that pulmonary infection is a primary complication of cystic fibrosis, the link between microbial diversity and a respiratory disorder was certainly obvious. From a conceptual perspective, however, the study of O'Connor *et al* published in this issue of *EBioMedicine* stands out as it clearly demonstrates that disruption of microbial diversity within the gut has more far reaching consequences as it is capable of disrupting the brain circuits that regulate breathing [2].

Although it is now well established that a broad range of respiratory and non-respiratory stressors (*e.g.* intermittent hypoxia, neonatal maternal separation, respectively) can impart plasticity in respiratory control, the link between changes in gut bacterial population dynamics and anomalies in respiratory reflexes is, at first, far from intuitive. However, in light of the recent wave of discoveries on microbiota-gut-brain signalling, this should not come as a surprise. To respiratory physiologists, the vagus nerve and its main projection site (the nucleus of the solitary tract) convey essential sensory signals to respiratory neurons; yet, these structures also happen to be the main pathways by which the bidirectional interactions between the gut and the brain take place [3]. Linking these concepts therefore makes for a novel and compelling hypothesis, but testing it rigorously is a different story.

To achieve this feat, O'Connor *et al* at University College Cork combined their expertise in respiratory physiology, nutrition, psychiatry, and microbiology to determine whether manipulation of gut microbiota composition alters cardiorespiratory function at rest and in response to respiratory challenges. This was accomplished using adult rats receiving broad-spectrum antibiotics (4 weeks) *vs.* vehicle controls, and antibiotic treated and untreated rats receiving subsequent faecal microbial transfer from healthy donors. To demonstrate treatment efficiency, the authors provide a thorough quantification of the dramatic changes in microbiota composition and diversity in the gut resulting from antibiotics and fecal transplant. The impact on respiratory function was then meticulously analysed in intact animals; the use of anesthetised animals facilitated quantification of arterial blood gases and cardiovascular variables.

Their demonstration that microbial manipulation had very specific consequences for respiratory function is remarkable and suggests that microbiota-gut-brain signalling has targeted effects on neural circuits for respiratory control (as opposed to non-specific outcomes). Microbial manipulation had no effect on breathing at rest, and attenuation of the hyperventilatory response to CO_2 was the most important change in respiratory control observed. By contrast, the effects of treatment on the ventilatory responses to hypoxia, either tested acutely or intermittently, were modest.

Considering the amount of work performed, this study is a goldmine of information. At a time when data reproducibility becomes a significant concern, this study raises important questions about the potential impact of diet and/or antibiotic administration on respiratory data. Furthermore, this study points to new and highly promising research avenues. For instance, data showing that the relative abundance of selected species of bacteria correlate with specific brainstem monoamines (but not noradrenaline or serotonin) raises the possibility that specific bacterial species could have profound effects on respiratory regulation.

In light of the growing interest for the beneficial effects of "psychobiotics" on mental health [4], one cannot help but wonder if manipulating the microbiota *via* ingestion of "highly desirable species" or faecal microbiota transplant (as is currently done for the treatment of gastro-intestinal disease) could become a valuable clinical treatment for respiratory disorders related to neural control dysfunction.

DOI of original article: https://doi.org/10.1016/j.ebiom.2019.03.029.
* Corresponding author.
E-mail address: richard.kinkead@fmed.ulaval.ca (R. Kinkead).

https://doi.org/10.1016/j.ebiom.2019.03.085

Considering that drastic changes in the gut microbiota have been observed in patients with multiple sclerosis [3] and that this population shows a reduced ventilatory response to CO_2 [5] akin to the results reported by O'Connor et al., this "gutsy idea" may not be that far-fetched. As a whole, this study reminds us once again that despite their robustness, the neural networks regulating breathing abide to the basic principles shaping the rest of the brain.

Disclosure

The author declared no competing interests.

References

[1] Sibley CD, Parkins MD, Rabin HR, Duan K, Norgaard JC, Surette MG. A polymicrobial perspective of pulmonary infections exposes an enigmatic pathogen in cystic fibrosis patients. Proc Natl Acad Sci 2008;105(39):15070–5.
[2] O'Connor KM, Lucking EF, Golubeva AV, Strain CR, Fouhy F, Cenit MC, et al. Manipulation of gut microbiota blunts the ventilatory response to hypercapnia in adult rats. EBioMedicine 2019;44:618–38.
[3] Fülling C, Dinan TG, Cryan JF. Gut microbe to brain signaling: what happens in vagus…. Neuron 2019;101(6):998–1002.
[4] Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ. Psychobiotics and the manipulation of bacteria–gut–brain signals. Trends Neurosci 2016;39(11):763–81.
[5] Tantucci C, Massucci M, Piperno R, Betti L, Grassi V, Sorbini CA. Control of breathing and respiratory muscle strength in patients with multiple sclerosis. Chest 1994;105(4):1163–70.